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(54) Title: SOLID PREPARATION

(57) Abstract: A solid preparation for oral administration, which suppresses decomposition of the active ingredient more completely and which is superior in preservation stability and free of problems in oral administration, can be obtained by producing a solid preparation containing ( )4-amino-5-chloro-2-ethoxy-N-[[4-(4-fluorobenzyl)-2-morpholinyl]methyl]benzamide or a salt thereof as a solid preparation substantially free of light anhydrous silicic acid, and preferably further containing low substituted hydroxypropylcellulose and/or free of film coating. More preferably, the solid preparation is a plain tablet.

DESCRIPTION

SOLID PREPARATION

Technical Field

The present invention relates to a stabilized solid preparation free of problems in oral administration, which contains, as an active ingredient, a compound, (±)4-amino-5-chloro-2-ethoxy-N-[[4-(4-fluorobenzyl)-2-morpholinyl]methyl]benzamide (hereinafter sometimes to be referred to as mosapride) or a salt thereof, which is a 5-HT4 receptor agonist and which is useful as an agent for the prophylaxis or treatment of symptoms in the digestive organs (heartburn, nausea, vomiting) associated with chronic gastritis, gastroesophageal reflux disease or gastrointestinal motility disturbance. The present invention also relates to a stabilized solid preparation free of light anhydrous silicic acid, and more preferably, further containing low substituted hydroxypropylcellulose. For another characteristic of the solid preparation of the present invention, the preparation is more preferably free of film coating.

Background Art

US patent No. 4870074 (JP-B-3-54937) describes benzamide derivatives and salts thereof, including mosapride and salts thereof, which are 5-HT4 receptor agonists.

This publication describes that the above-mentioned compound and a salt thereof show a gastrointestinal function promoting action but show weak side effects on the central nervous system, and therefore, are superior compounds as pharmaceutical agents. In addition, US Patent No. 4870074 discloses a preparation containing light anhydrous silicic acid (aerosil) and microcrystalline cellulose in addition to lactose, cornstarch, hydroxypropylcellulose and magnesium stearate, as an example of a mosapride-containing preparation.

In Japan etc, mosapride citrate-containing preparations

have been marketed under the trade names of Gasmotin and the like as drugs applicable to symptoms in the digestive organs (heartburn, nausea, vomiting) associated with chronic gastritis, but these preparations are film-coated preparations. Also, cisapride, which is the same 5-HT4 receptor agonist, has been marketed in the form of a film coated preparation.

There is a demand for a superior formulation for a pharmaceutical agent for the prophylaxis or treatment of gastroesophageal reflux disease or gastrointestinal motility disturbance, which contains mosapride, which is a 5-HT4 receptor agonist, or a salt thereof, wherein production of decomposition by-product of the active ingredient and the like have been more completely suppressed, decomposition of the active ingredient is suppressed even when preserved for a long time, thereby avoiding decrease in the content, the preservation stability is further improved, and a bitter taste is suppressed, thereby obliterating problems in oral administration.

Disclosure of the Invention

The present inventors have conducted various studies with the aim of producing a preparation having more superior stability of the above-mentioned mosapride or a salt thereof, produced a preparation without a film coating, though film coating was considered to be essential because of the bitter taste of mosapride and a salt thereof, and found that decomposition of mosapride can be suppressed, a decomposed substance is not produced during long-term preservation, and a superior preparation free of problems in oral administration can be obtained by combining suitable excipients or additives. Further studies have led to the finding that, particularly a preparation substantially free of light anhydrous silicic acid suppresses decomposition of mosapride and a salt thereof and provides a stabilized preparation, and still further studies

have resulted in the completion of the present invention.

Accordingly, the present invention provides the following (1)-(13).

(1) A solid preparation (except orally disintegrating tablets) free of film coating, which is substantially free of light anhydrous silicic acid and which comprises (±)4-amino-5-chloro-2-ethoxy-N-[[4-(4-fluorobenzyl)-2-morpholinyl]methyl]benzamide or a salt thereof.

(2) The solid preparation of the above-mentioned (1), which is a plain tablet.

(3) The solid preparation of the above-mentioned (1), which comprises low substituted hydroxypropylcellulose.

(4) The solid preparation of any of the above-mentioned (1) to (3), further comprising hydroxypropylcellulose.

(5) The solid preparation of the above-mentioned (4), further comprising lactose and/or cornstarch.

(6) The solid preparation of the above-mentioned (5), which is a tablet.

(7) The solid preparation of the above-mentioned (6), which comprises magnesium stearate.

(8) The solid preparation of any of the above-mentioned (1) to (7), wherein the (±)4-amino-5-chloro-2-ethoxy-N-[[4-(4-fluorobenzyl)-2-morpholinyl]methyl]benzamide or a salt thereof is (±)4-amino-5-chloro-2-ethoxy-N-[[4-(4-fluorobenzyl)-2-morpholinyl]methyl]benzamide citrate dihydrate.

(9) A commercial package comprising the solid preparation of the above-mentioned (1) and a written matter associated therewith, the written matter stating that the solid preparation can or should be used for preventing or treating gastroesophageal reflux disease (GERD) or promoting gastrointestinal motility.

(10) A solid preparation free of film coating, which comprises (±)4-amino-5-chloro-2-ethoxy-N-[[4-(4-fluorobenzyl)-2-

morpholinyl]methyl]benzamide or a salt thereof and further a disintegrator selected from low substituted hydroxypropylcellulose, crosscarmellose sodium, carmellose calcium and crospovidone.

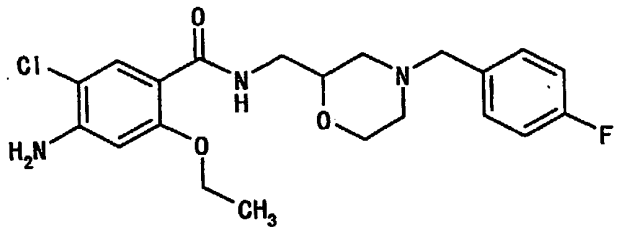
(11) The solid preparation of the above-mentioned (10), wherein the disintegrator is low substituted hydroxypropylcellulose.

(12) A solid preparation, which is substantially free of light anhydrous silicic acid, and which comprises (±)4-amino-5-chloro-2-ethoxy-N-[[4-(4-fluorobenzyl)-2-morpholinyl]methyl]benzamide or a salt thereof and low substituted hydroxypropylcellulose.

(13) A solid preparation which is substantially free of light anhydrous silicic acid, and which comprises (±)4-amino-5-chloro-2-ethoxy-N-[[4-(4-fluorobenzyl)-2-morpholinyl]methyl]benzamide or a salt thereof.

Detailed Description of the Invention

Mosapride or (±)4-amino-5-chloro-2-ethoxy-N-[[4-(4-fluorobenzyl)-2-morpholinyl]methyl]benzamide, which is the active ingredient of the preparation of the present invention, is represented by the formula



It has a gastrointestinal function promoting action as a 5-HT4 receptor agonist, and is known as an antiemetic and a drug for the prophylaxis or treatment of symptoms in the digestive organs (heartburn, nausea, vomiting) associated with chronic gastritis. Moreover, the stabilized preparation of the present invention is also useful as a drug for the prophylaxis or

treatment of gastroesophageal reflux disease (GERD) and the like, based on the 5-HT4 receptor agonist action and gastrointestinal function promoting action of mosapride.

The active ingredient of the present invention may be a salt of mosapride, and as such salt, a physiologically acceptable salt is preferable, and an acid addition salt is particularly preferable. As the salt, for example, organic acid salts such as salts with acetic acid, formic acid, propionic acid, fumaric acid, maleic acid, succinic acid, tartaric acid, citric acid, malic acid, oxalic acid, benzoic acid, lactic acid, methanesulfonic acid, benzenesulfonic acid, and the like, inorganic acid salts such as hydrochloride, hydrobromide, hydroiodide, sulfate, phosphate and the like can be mentioned. As the salt of mosapride, an organic acid salt is generally preferable, and citrate is particularly preferable.

In the present invention, a prodrug of mosapride or a salt thereof may be used as a main ingredient, instead of mosapride and a salt thereof.

The prodrug of mosapride having a 5-HT4 receptor agonist action, which is used in the present invention, refers to a compound that converts into mosapride having a 5-HT4 receptor agonist action as a result of reaction with an enzyme, gastric acid and the like under physiological conditions in living organisms, such as a compound that converts into mosapride having a 5-HT4 receptor agonist action due to enzymatic oxidization, reduction, hydrolysis etc and a compound that converts into mosapride having a 5-HT4 receptor agonist action due to hydrolysis and the like by gastric acid and the like. As the prodrug of mosapride, a compound wherein amino group of mosapride having a 5-HT4 receptor agonist action is acylated, alkylated or phosphorylated (e.g., a compound wherein amino group of mosapride having a 5-HT4 receptor agonist action is

eicosanoylated, alanylated, pentylaminocarbonylated, (5-methyl-2-oxo-1,3-dioxolene-4-yl)methoxycarbonylated, tetrahydrofuranylated, pyrolidylmethylated, pivaloyloxymethylated or tert-butylated, and the like) and the like can be mentioned. These compounds can be produced from mosapride by a method known *per se*.

A prodrug of mosapride having a 5-HT4 receptor agonist action may be a compound which is converted into mosapride having a 5-HT4 receptor agonist action under the physiological conditions, as described in Development of Pharmaceutical Product, vol. 7 molecule design pp. 163 - 198, Hirokawa Shoten (1990).

Mosapride, a salt thereof and a prodrug thereof may be solvates. Thus, "mosapride, a salt thereof or a prodrug thereof" in the present specification encompasses their solvates. The solvate may be a hydrate or non-hydrate solvate, with preference given to hydrate.

The hydrate may be a 0.2 to 3 hydrate, with particular preference given to dihydrate.

As a preparation for the prophylaxis or treatment of gastroesophageal reflux disease (GERD), mosapride citrate dihydrate (hereinafter sometimes to be referred to as compound A) is preferably used.

Mosapride or a salt thereof to be the active ingredient in the present invention can be produced according to a known production method described in US Patent No. 4870074 or an analogous method.

The content of the mosapride or a salt thereof (including solvates such as hydrate thereof and the like) or a prodrug thereof (hereinafter sometimes to be referred to as an active ingredient) in the preparation of the present invention is about 0.01 - about 100 weight (w/w)%, preferably about 0.5 - about 70 w/w%, more preferably about 0.5 - about 50 w/w%,

still more preferably about 0.5 - about 30 w/w%, of the entire preparation, based on mosapride.

The present inventors have conducted intensive studies in pursuit of a preparation more stably containing the active ingredient, mosapride, a salt thereof or the like, and found that, although a preparation of mosapride, a salt thereof or the like is considered to essentially require film coating from the aspect of easy oral administration, particularly for correction of the taste, a film coated preparation unexpectedly accompanies production of a relative substance, particularly a metabolite or a decomposed product, of mosapride in an accelerated stability test, and therefore, in the case of a film coated preparation, packaging should be specially designed to ensure stabilization, and that a solid preparation free of film coating further suppresses production of decomposed by-product and the like of mosapride or a salt thereof. In addition, various investigations of excipients and additives that do not destabilize or decompose the active ingredient have unexpectedly revealed that a preparation free of light anhydrous silicic acid is preferable. The preparation of the present invention is characterized in that it does not substantially contain light anhydrous silicic acid (aerosil and the like) frequently used for tablets. In general, light anhydrous silicic acid when added as a fluidity modulator and the like is considered to not cause a chemical change with other substances. In the case of a preparation comprising mosapride, a salt thereof and the like, however, it has been found that the active ingredient (mosapride, a salt thereof etc.) is more stabilized and is not decomposed easily in a preparation substantially free of light anhydrous silicic acid than in a preparation containing light anhydrous silicic acid. The preparation of the present invention is required to be substantially free of light anhydrous silicic acid, and a

trace amount thereof may be contained, as long as the active ingredient is substantially free of an adverse influence on stability and the like. In particular, a preparation that does not contain light anhydrous silicic acid in a proportion of not less than 0.25 w/w%, preferably not less than 0.2 w/w%, of the total amount of the preparation is preferable. Moreover, a preparation wherein its content is suppressed to not more than 0.1 w/w% is preferable. When productivity is free of problems in industrial production even without addition of a fluidizer, light anhydrous silicic acid is preferably not combined.

In the case of a preparation containing light anhydrous silicic acid or a film coated preparation, desirably, stabilization may be secured by a designed packaging and the like, since interaction with the active ingredient, mosapride, a salt thereof etc. sometimes leads to the production of a decomposed product, depending on the preservation conditions. By affording a final preparation free of light anhydrous silicic acid or film coating, a preparation superior in long-term preservation stability can be obtained. As a result, a special packaging form aiming at stabilization and a step for film coating during production of the preparation are not necessary, which is highly advantageous for industrial production and from the economical aspect.

When a disintegrator selected from the group consisting of low substituted hydroxypropylcellulose, crosscarmellose sodium, carmellose calcium and crospovidone, preferably low substituted hydroxypropylcellulose, is used as a disintegrator capable of suppressing a bitter taste and the like caused by the absence of film coating, and combined with other excipients and carriers, the bitter taste can be sufficiently suppressed even without film coating, thereby affording a preparation free of problems in oral administration. A preparation using low substituted hydroxypropylcellulose,

crosscarmellose sodium, carmellose calcium or crospovidone as a disintegrator has been found to be preferable in terms of dissolution property, disintegration property, combinability with the active ingredient and the like, in addition to capability of suppressing a bitter taste.

For example, the above-mentioned US Patent No. 4870074 describes an example of a preparation comprising mosapride. When compared with the preparation in the example using microcrystalline cellulose, the preparation of the present invention using low substituted hydroxypropylcellulose is superior in dissolution property and disintegration property. That is, most of the components are completely dissolved immediately after the start of dissolution of the active ingredient, where dissolution does not take a long time and an undissolved part does not remain. Low substituted hydroxypropylcellulose is superior in combinability with mosapride, because a decomposed product of mosapride is not produced for a long time when it is combined with mosapride or a salt thereof.

As the low substituted hydroxypropylcellulose to be used in the preparation of the present invention, any low substituted hydroxypropylcellulose generally used as a preparation excipient such as disintegrator, binder and the like may be used, and low substituted hydroxypropylcellulose having a degree of substitution of about 4 to 20, namely, a hydroxypropoxy group content of about 4-20%, and improved products thereof can be used. Low substituted hydroxypropylcellulose having a hydroxypropoxy group content of about 7-16% is available from the market and convenient. A special low substituted hydroxypropylcellulose having a hydroxypropoxy group content of about 5-7% may be also used. While the particle size of low substituted hydroxypropylcellulose is not particularly limited, one having

an average particle size of not more than 200 μm is generally used. Preferably, one having an average particle size of not more than 150 μm is preferable for production.

While the amount of low substituted hydroxypropylcellulose to be combined is not particularly limited, it is preferably from about 0.05 to about 1000 w/w%, more preferably from about 0.3 to about 800 w/w%, particularly from about 100 to about 600 w/w%, of the active ingredient mosapride, a salt thereof or the like (including solvate such as hydrate thereof and the like). It is preferably from about 1 to about 40 w/w%, more preferably 5 - 30 w/w%, particularly about 20 w/w%, of the total amount of the preparation. When crosscarmellose sodium, carmellose calcium, crospovidone and the like are used as disintegrators, they can be added in an amount according to the above-mentioned amount of low substituted hydroxypropylcellulose.

The solid preparation of the present invention encompasses preparations in the dosage form of, for example, tablet, powder, fine granules, granule, capsule and the like.

The preparation of the present invention may contain various excipients, additives, carriers and the like conventionally used as components of a solid preparation.

In particular, from the aspects of combinability with the active ingredient, economic efficiency, safety, stability, easy availability and the like, a combination of low substituted hydroxypropylcellulose, lactose and cornstarch as a disintegrator is preferable. As the binder, hydroxypropylcellulose is preferably used. When the solid preparation of the present invention is a tablet, magnesium stearate is preferably combined as a lubricant.

According to the present invention, a disintegrator such as low substituted hydroxypropylcellulose, crosscarmellose sodium, carmellose calcium, Crospovidone and the like,

preferably low substituted hydroxypropylcellulose, is combined, and if necessary, lactose, cornstarch and hydroxypropylcellulose are combined, and depending on the dosage form, excipients and additives such as magnesium stearate and the like are combined to give a preparation. As a result, the bitter taste peculiar to the active ingredient is unexpectedly reduced even if film coating is not applied, and a stable mosapride preparation can be provided, which is free of problems in oral administration, shows suppression of decomposition of the active ingredient, mosapride, a salt thereof or the like, and which is free of decrease in the content and the like for a long time.

The amount of lactose to be combined is generally about 10 - 95 w/w%, preferably about 20 - 80 w/w%, more preferably about 30 - 50 w/w%, relative to the total amount of the preparation.

The amount of cornstarch to be combined is generally about 5 - 50 w/w%, preferably 10 - 40 w/w%, more preferably about 25 w/w%, relative to the total amount of the preparation.

The amount of hydroxypropylcellulose to be combined is generally about 0.5 - 10 w/w%, preferably about 1 - 5 w/w%, more preferably about 2 w/w%, relative to the total amount of the preparation.

The amount of magnesium stearate to be combined is generally about 0.1 - 5 w/w%, preferably about 0.3 - 3 w/w%, more preferably about 1 w/w%, relative to the total amount of the preparation.

The preparation of the present invention may contain additives and carriers conventionally used for producing solid pharmaceutical preparations, particularly pharmacologically acceptable carriers and additives, in addition to the above-mentioned components, as long as there is no particular inconvenience. As such additives and carriers, various organic

and inorganic carriers conventionally used as materials for preparations can be mentioned, such as excipients, lubricants, binders and disintegrators for solid preparations. As the excipient, for example, sucrose, D-mannitol, starch, microcrystalline cellulose and the like can be mentioned. As the binder, for example, pregelatinized starch, sucrose, gelatin, gum arabic powder, methyl cellulose, carboxymethyl cellulose, carboxymethyl cellulose sodium, hydroxypropylmethyl cellulose, polyvinylpyrrolidone, microcrystalline cellulose, dextrin, pullulan and the like are used; as the lubricant, for example, calcium stearate, talc, colloidal silica and the like are used; and as the disintegrator, for example, sucrose, starch (potato starch and the like), carboxymethyl starch sodium and the like are used, in addition to or in the place of the above-mentioned low substituted hydroxypropylcellulose, crosscarmellose sodium, carmellose calcium, crospovidone and the like. Where necessary, other stabilizers, preservatives, antioxidants (e.g., L-ascorbic acid, L-cysteine, sulfite, α-tocopherol etc.), coloring agents, shading agents such as pigments (e.g., titanium dioxide, red ferric oxide, yellow ferric oxide etc.) and the like, corrigents, sweeteners, absorbents, preservatives, humectants, antistatic agents, disintegration extending agents, inorganic salts (e.g., magnesium carbonate, calcium carbonate etc.) and the like may be added.

The solid preparation of the present invention can be produced according to a known method (e.g., the method described in the Pharmacopoeia of Japan, 10th Edition, Preparation General Provision). For example, various components mentioned above are admixed homogeneously, and the mixture is processed into a preparation by a known method. For example, various solid preparations suitable for oral administration, such as tablet, capsule, powder, dry syrup,

granules, fine granules, pill and the like can be prepared. In the case of tablet, for example, mosapride or a salt thereof, excipients, disintegrators and the like are added, mixed, a binder is added to give granules, to which lubricants and disintegrators are added and the mixture is tableted to give tablets. Granules can be also produced by press granulation according to a method almost similar to the production of tablet or by fluidized bed granulation. The particle size distribution of granules is, for example, not less than 90 weight % for particles having a particle size of 500-1410 μm and not more than 5 weight % for particles having a particle size of not more than 177 μm. The particle size distribution of fine granules is, for example, not less than 75 weight % for particles having a particle size of 10-500 μm, not more than 5 weight % for particles having a particle size of not less than 500 μm and not more than 10 weight % for particles having a particle size of not more than 10 μm. The preferable particle size distribution of fine granules is not less than 75 weight % for particles having a particle size of 105-500 μm, not more than 5 weight % for particles having a particle size of not less than 500 μm, and not more than 10 weight % for particles having a particle size of not more than 74 μm.

As the solid preparation of the present invention, a tablet without film coating is particularly preferable. The tablet without film coating may be a sugar-coated tablet, but plain tablet and/or naked tablet are/is generally preferable from the aspects of economical efficiency and industrial productivity.

Because the preparation *per se* of the present invention has been stabilized, it can be processed into a final product in any packaging form generally employed for a solid preparation. When a preparation free of film coating is to be produced, a packaging form suitable for a preparation without

film coating, a plain tablet or a naked product is preferably employed depending on the object.

Since mosapride, a salt thereof (including solvate such as hydrate thereof and the like) and the like to be the active ingredient in the present invention show low toxicity and are safe 5-HT4 receptor agonists, the solid preparation of the present invention stably containing these active ingredients can be used as, for example, 5-HT4 receptor agonists, for various pharmaceutical uses in mammals (e.g., mouse, rat, hamster, rabbit, cat, dog, bovine, sheep, monkey, human etc.). For example, they have a gastrointestinal motility (function) promoting action and a gastric emptying action and are useful as agents for the prophylaxis or treatment of gastroesophageal reflux disease (GERD; including reflux esophagitis), diseases in gastroesophageal reflux free of esophagitis (Symptomatic Gastroesophageal Reflux Disease (Symptomatic GERD)), symptoms in the digestive organs (heartburn, nausea, vomiting) associated with chronic gastritis, non-ulcer dyspepsia, constipation type irritable bowel syndrome (Irritable Bowel Syndrome (IBS)), diarrhea type irritable bowel syndrome (Irritable Bowel Syndrome (IBS)), NUD (Non Ulcer Dyspepsia) and the like. Of these, they can be used as prophylactic or therapeutic drugs for gastroesophageal reflux disease (GERD) or gastrointestinal motility disturbance or antiemetic, and as stable preparations of mosapride or a salt thereof, which are not easily denatured and show efficacy in patients with these diseases.

The compound of the present invention may be used concurrently with other active ingredients. For combined use, it is generally preferably used together with 1 to 3 kinds of active ingredients.

As said "other active ingredients", for example, proton pump inhibitors (lansoprazole, omeprazole, rabeprazol,

pantoprazole, timoprazol and the like), histamine H2-receptor antagonists (cimetidine, famotidine and the like), other digestive organ function promoting agents, antimicrobial agents (e.g., substances with anti-helicobacter pylori activity, imidazole compounds, bismuth salts, quinolone compounds etc.), antacids, antitumor agents, anti-inflammatory drugs such as non-steroidal anti-inflammatory drug (NSAID) etc, and the like can be mentioned.

As the "substances with anti-helicobacter pylori activity", for example, antibiotic penicillin (e.g., amoxicillin, benzylpenicillin, piperacillin, mecillinam etc.), antibiotic cefem (e.g., cefixime, cefaclor etc.), antibiotic macrolide (e.g., erythromycin, clarithromycin etc.), tetracycline antibiotic (e.g., tetracycline, minocycline, streptomycin etc.), antibiotic aminoglycoside (e.g., gentamicin, amikacin etc.), imipenem and the like can be mentioned. Of these, antibiotic penicillin, antibiotic macrolide and the like are preferable.

As the "imidazole compounds", for example, metronidazole, miconazole and the like can be mentioned.

As the "bismuth salts", for example, bismuth acetate, bismuth citrate and the like can be mentioned.

As the "quinolone compounds", for example, ofloxacin, ciploxacin and the like can be mentioned.

The "other active ingredients" and mosapride, a salt thereof (including solvate such as hydrate thereof and the like) or the like to be the active ingredient in the present invention may be mixed according to a method known *per se*, and used in combination as a single pharmaceutical composition (e.g., tablet, powder, granule, capsule (including soft capsule), sustained-release preparation etc.), or each may be prepared separately and administered to the same subject simultaneously or in a staggered manner in time. Other active

ingredients may be administered orally or parenterally (injection, suppositories etc.).

While the dose of the solid preparation of the present invention varies depending on the administration subject, disease and the like, when it is administered as an oral agent for the prophylaxis or treatment of, for example, Gastroesophageal Reflux Disease (GERD) in an adult (body weight 60 kg), mosapride or a salt thereof (including solvate such as hydrate thereof and the like) can be administered in a daily dose of the active ingredient of about 0.1 - about 100 mg, preferably about 0.5 - about 80 mg, more preferably about 1 - about 70 mg, which is administered at once or in several portions a day. Generally, about 3.0 mg - about 60 mg is preferably administered to an adult in about 3 portions a day.

As the preparation of the present invention, therefore, a tablet containing about 1 mg - about 20 mg of the active ingredient of mosapride or a salt thereof (including solvate such as hydrate thereof and the like) is particularly preferable for oral administration.

The present invention is explained in detail in the following by referring to Examples, which are not to be construed as limitative.

As cornstarch, hydroxypropylcellulose (HPC-L), magnesium stearate, lactose and low substituted hydroxypropylcellulose to be used in the following Examples, the products acceptable according to the Pharmacopoeia of Japan, 14th Edition, were used and as red ferric oxide and yellow ferric oxide, those acceptable according to the pharmaceutical product additive standard were used.

Examples

Example 1

Hydroxypropylcellulose (104 g) was dissolved in purified water (1628 g). Red ferric oxide (5.2 g) and yellow ferric

oxide (10.4 g) were dispersed in the obtained solution to give a binder dispersion.

Compound A or (±)4-amino-5-chloro-2-ethoxy-N-[[4-(4-fluorobenzyl)-2-morpholinyl]methyl]benzamide citrate dihydrate (212.8 g), lactose (2476 g) and cornstarch (1300 g) were uniformly mixed in a fluidized bed granulation dryer (FD-5S, POWREX CORPORATION), and the binder dispersion was sprayed for granulation, which granules were then dried in the fluidized bed granulation dryer.

The obtained granules were crushed using a power mill grinding machine (P-3, Showa Chemical Machine Kousakusho) and a 1.5 mmϕ punching screen to give particles having a regulated size.

To the resulting particles having a regulated size (2568 g) were added low substituted hydroxypropylcellulose (650 g) and magnesium stearate (32.5 g), and they were admixed in a tumbler mixer (TM-15, Showa Chemical Machine Kousakusho) to give granules for tableting. The obtained granules were tableted in a rotary tableting machine (Correct12HUK, Kikusui Seisakusho Ltd.) using a 7.0 mmϕ punch at weight 130 mg (tableting pressure 9.5 KN/punch) to give tablets having the following formulation, which contained 5.29 mg of compound A per tablet.

Formulation (composition per tablet):

1) Compound A	5.29	mg
2) Lactose	61.92	mg
3) Cornstarch	32.5	mg
4) Hydroxypropylcellulose	2.6	mg
5) Red ferric oxide	0.13	mg
6) Yellow ferric oxide	0.26	mg
7) Low substituted hydroxypropylcellulose	26.0	mg
8) Magnesium stearate	1.3	mg
Total	130.0	mg

Example 2

When the tablets obtained in Example 1 were preserved in a sealed glass bottle at 40°C for 3 months, and when they were preserved in an open-seal glass bottle at 40°C and 75%RH for 3 months, production of relative substances at a level of not less than the quantitation limit (0.05%) was not observed and the tablets were stable.

Example 3

In the same manner as in Example 1 except that the amounts of compound A and lactose were set for 425.7 g and 2263 g, respectively, tablets having the following formulation, which contained 10.59 mg of compound A per tablet were obtained.

Formulation (composition per tablet):

1) Compound A	10.59	mg
2) Lactose	56.62	mg
3) Cornstarch	32.5	mg
4) Hydroxypropylcellulose	2.6	mg
5) Red ferric oxide	0.13	mg
6) Yellow ferric oxide	0.26	mg
7) Low substituted hydroxypropylcellulose	26.0	mg
8) Magnesium stearate	1.3	mg
Total	130.0	mg

Example 4

In the same manner as in Example 1 except that the amounts of compound A and lactose were set for 851.3 g and 1837 g, respectively, tablets having the following formulation, which contained 21.17 mg of compound A per tablet were obtained.

Formulation (composition per tablet):

1) Compound A	21.17	mg
2) Lactose	46.04	mg
3) Cornstarch	32.5	mg

4) Hydroxypropylcellulose	2.6	mg
5) Red ferric oxide	0.13	mg
6) Yellow ferric oxide	0.26	mg
7) Low substituted hydroxypropylcellulose	26.0	mg
8) Magnesium stearate	1.3	mg
Total	130.0	mg

Example 5

Hydroxypropylcellulose (1352 g) was dissolved in purified water (25490 g). Red ferric oxide (67.6 g) and yellow ferric oxide (135.2 g) were dispersed in the obtained solution to give a binder dispersion.

Compound A (2775 g), lactose (32170 g) and cornstarch (16900 g) were uniformly mixed in a fluidized bed granulation dryer (WSG-60, POWREX CORPORATION), and the binder dispersion was sprayed for granulation, which granules were then dried in the fluidized bed granulation dryer.

The obtained granules were crushed using a power mill grinding machine (P-7S, Showa Chemical Machine Kousakusho) and a 1.5 mmϕ punching screen to give particles having a regulated size.

To the resulting particles having a regulated size (48990 g) were added low substituted hydroxypropylcellulose (12400 g) and magnesium stearate (620.1 g), and they were admixed in a tumbler mixer (TM-400s, Showa Chemical Machine Kousakusho) to give granules for tableting. The obtained granules were tableted in a rotary tableting machine (AQUA 0836SS2JII-B0CCG3, Kikusui Seisakusho Ltd.) using a 7.0 mmϕ punch at weight 130 mg (tableting pressure 9.5 KN/punch) to give tablets having the following formulation, which contained 5.29 mg of compound A per tablet.

Formulation (composition per tablet):

1) Compound A	5.29	mg
2) Lactose	61.92	mg

3) Cornstarch	32.5	mg
4) Hydroxypropylcellulose	2.6	mg
5) Red ferric oxide	0.13	mg
6) Yellow ferric oxide	0.26	mg
7) Low substituted hydroxypropylcellulose	26.0	mg
8) Magnesium stearate	1.3	mg
Total	130.0	mg

Example 6

In the same manner as in Example 5 except that the amounts of compound A and lactose were set for 5550 g and 29400 g, respectively, tablets having the following formulation, which contained 10.59 mg of compound A per tablet were obtained.

Formulation (composition per tablet):

1) Compound A	10.59	mg
2) Lactose	56.62	mg
3) Cornstarch	32.5	mg
4) Hydroxypropylcellulose	2.6	mg
5) Red ferric oxide	0.13	mg
6) Yellow ferric oxide	0.26	mg
7) Low substituted hydroxypropylcellulose	26.0	mg
8) Magnesium stearate	1.3	mg
Total	130.0	mg

Example 7

In the same manner as in Example 5 except that the amounts of compound A and lactose were set for 11100 g and 23850 g, respectively, tablets having the following formulation, which contained 21.17 mg of compound A per tablet were obtained.

Formulation (composition per tablet):

1) Compound A	21.17	mg
2) Lactose	46.04	mg
3) Cornstarch	32.5	mg

4) Hydroxypropylcellulose	2.6	mg
5) Red ferric oxide	0.13	mg
6) Yellow ferric oxide	0.26	mg
7) Low substituted hydroxypropylcellulose	26.0	mg
8) Magnesium stearate	1.3	mg
Total	130.0	mg

Example 8

Hydroxypropylcellulose (104 g) is dissolved in purified water (1628 g) to give a binder dispersion.

Compound A (211.6 g), lactose (2492 g) and cornstarch (1300 g) are uniformly mixed in a fluidized bed granulation dryer (FD-5S, POWREX CORPORATION), and the binder dispersion is sprayed for granulation, which granules are then dried in the fluidized bed granulation dryer.

The obtained granules are crushed using a power mill grinding machine (P-3, Showa Chemical Machine Kousakusho) and a 1.5 mmϕ punching screen to give particles having a regulated size.

To the resulting particles having a regulated size (2568 g) are added low substituted hydroxypropylcellulose (650 g) and magnesium stearate (32.5 g), and they are admixed in a tumbler mixer (TM-15, Showa Chemical Machine Kousakusho) to give granules for tableting. The obtained granules are tableted in a rotary tableting machine (Correct12HUK, Kikusui Seisakusho Ltd.) using a 7.0 mmϕ punch at weight 130 mg (tableting pressure 9.5 KN/punch) to give tablets having the following formulation, which contain 5.29 mg of compound A per tablet.

Formulation (composition per tablet):

1) Compound A	5.29	mg
2) Lactose	62.31	mg
3) Cornstarch	32.5	mg
4) Hydroxypropylcellulose	2.6	mg

5) Low substituted hydroxypropylcellulose	26.0	mg
6) Magnesium stearate	1.3	mg
Total	130.0	mg

Example 9

Hydroxypropylcellulose (104 g) is dissolved in purified water (1628 g). Yellow ferric oxide (10.4 g) is dispersed in the obtained solution to give a binder dispersion.

Compound A (423.6 g), lactose (2270 g) and cornstarch (1300 g) are uniformly mixed in a fluidized bed granulation dryer (FD-5S, POWREX CORPORATION), and the binder dispersion is sprayed for granulation, which granules are then dried in the fluidized bed granulation dryer.

The obtained granules are crushed using a power mill grinding machine (P-3, Showa Chemical Machine Kousakusho) and a 1.5 mmϕ punching screen to give particles having a regulated size.

To the resulting particles having a regulated size (2568 g) are added low substituted hydroxypropylcellulose (650 g) and magnesium stearate (32.5 g), and they are admixed in a tumbler mixer (TM-15, Showa Chemical Machine Kousakusho) to give granules for tableting. The obtained granules are tableted in a rotary tableting machine (Correct12HUK, Kikusui Seisakusho Ltd.) using a 7.0 mmϕ punch at weight 130 mg (tableting pressure 9.5 KN/punch) to give tablets having the following formulation, which contain 5.29 mg of compound A per tablet.

Formulation (composition per tablet):

1) Compound A	10.59	mg
2) Lactose	56.75	mg
3) Cornstarch	32.5	mg
4) Hydroxypropylcellulose	2.6	mg
5) Yellow ferric oxide	0.26	mg
6) Low substituted hydroxypropylcellulose	26.0	mg

7) Magnesium stearate	1.3	mg
Total	130.0	mg

Example 10

Hydroxypropylcellulose (104 g) is dissolved in purified water (1628 g). Red ferric oxide (1.2 g) is dispersed in the obtained solution to give a binder dispersion.

Compound A (846.8 g), lactose (1856 g) and cornstarch (1300 g) are uniformly mixed in a fluidized bed granulation dryer (FD-5S, POWREX CORPORATION), and the binder dispersion is sprayed for granulation, which granules are then dried in the fluidized bed granulation dryer.

The obtained granules are crushed using a power mill grinding machine (P-3, Showa Chemical Machine Kousakusho) and a 1.5 mmϕ punching screen to give particles having a regulated size.

To the resulting particles having a regulated size (2568 g) are added low substituted hydroxypropylcellulose (650 g) and magnesium stearate (32.5 g), and they are admixed in a tumbler mixer (TM-15, Showa Chemical Machine Kousakusho) to give granules for tableting. The obtained granules are tableted in a rotary tableting machine (Correct12HUK, Kikusui Seisakusho Ltd.) using a 7.0 mmϕ punch at weight 130 mg (tableting pressure 9.5 KN/punch) to give tablets having the following formulation, which contain 21.17 mg of compound A per tablet.

Formulation (composition per tablet):

1) Compound A	21.17	mg
2) Lactose	46.4	mg
3) Cornstarch	32.5	mg
4) Hydroxypropylcellulose	2.6	mg
5) Red ferric oxide	0.03	mg
6) Low substituted hydroxypropylcellulose	26.0	mg
7) Magnesium stearate	1.3	mg

Total	130.0 mg

Industrial Applicability

Inasmuch as the solid preparation of the present invention can be used advantageously for the prophylaxis or treatment of gastroesophageal reflux disease (GERD), a disease of gastrointestinal motility disturbance and the like as a stable preparation free of easy decomposition of the active ingredient (mosapride or a salt thereof) showing efficacy in these diseases and decrease in the contents even in a long-term preservation, it is of pharmaceutical industrial use.

This application is based on patent application No. 023363/2003 filed in Japan, the contents of which are hereby incorporated by reference.

CLAIMS

1. A solid preparation (except orally disintegrating tablets) free of film coating, which is substantially free of light anhydrous silicic acid and which comprises (±)4-amino-5-chloro-2-ethoxy-N-[[4-(4-fluorobenzyl)-2-morpholinyl]methyl]benzamide or a salt thereof.

2. The solid preparation of claim 1, which is a plain tablet.

3. The solid preparation of claim 1, which comprises low substituted hydroxypropylcellulose.

4. The solid preparation of any of claims 1 to 3, further comprising hydroxypropylcellulose.

5. The solid preparation of claim 4, further comprising lactose and/or cornstarch.

6. The solid preparation of claim 5, which is a tablet.

7. The solid preparation of claim 6, which comprises magnesium stearate.

8. The solid preparation of any of claims 1 to 7, wherein the (±)4-amino-5-chloro-2-ethoxy-N-[[4-(4-fluorobenzyl)-2-morpholinyl]methyl]benzamide or a salt thereof is (±)4-amino-5-chloro-2-ethoxy-N-[[4-(4-fluorobenzyl)-2-morpholinyl]methyl]benzamide citrate dihydrate.

9. A commercial package comprising the solid preparation of claim 1 and a written matter associated therewith, the written matter stating that the solid preparation can or should be

used for preventing or treating gastroesophageal reflux disease (GERD) or promoting gastrointestinal motility.

10. A solid preparation free of film coating, which comprises (±)4-amino-5-chloro-2-ethoxy-N-[[4-(4-fluorobenzyl)-2-morpholinyl]methyl]benzamide or a salt thereof, and further a disintegrator selected from low substituted hydroxypropylcellulose, crosscarmellose sodium, carmellose calcium and crospovidone.

11. The solid preparation of claim 10, wherein the disintegrator is low substituted hydroxypropylcellulose.

12. A solid preparation, which is substantially free of light anhydrous silicic acid, and which comprises (±)4-amino-5-chloro-2-ethoxy-N-[[4-(4-fluorobenzyl)-2-morpholinyl]methyl]benzamide or a salt thereof and low substituted hydroxypropylcellulose.